ORIGINAL ARTICLE

Risk of long term renal impairment and duration of follow up recommended for Henoch-Schönlein purpura with normal or minimal urinary findings: a systematic review

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Background: The duration of follow up to assess the risk of long term renal impairment in Henoch-Schönlein purpura (HSP) without nephritic or nephrotic syndrome or renal failure on diagnosis remains undetermined.

Aims: To undertake a systematic review of the literature to assess whether the risk of long term renal impairment without renal involvement on diagnosis could be estimated and to determine the time period when renal involvement is very unlikely after the diagnosis of HSP.

Methods: Search of studies of unselected children with HSP, and available information on urinary findings, renal involvement, and long term renal function follow up. Studies of selected children with HSP nephropathy at diagnosis were excluded.

Results: Twelve studies of 1133 children were reviewed. The follow up period ranged from 6 weeks to 36 years. Proteinuria and/or haematuria, which occurred in 34.2%, of which only one fifth were in association with nephritic or nephrotic syndrome, developed in 85% of cases within 4 weeks of the diagnosis of HSP, in 91% within 6 weeks, and in 97% within 6 months. Permanent renal impairment never developed after normal urinalysis; it occurred in 1.6% of those with isolated urinary abnormalities, and in 19.5% of those who developed nephritic or nephrotic syndrome.

Conclusion: No long term renal impairment occurred after normal urinalysis. Even if urinalysis is normal at presentation, the testing should be continued for six months. There is no need to follow up after the first six months those whose urinalysis remains normal.

Henoch-Schönlein purpura (HSP) is a non-thrombocytopenic systemic hypersensitivity vasculitis of childhood. Its aetiology remains largely unknown, and the prognosis, although generally very good, depends primarily on the extent of renal involvement.

The primary long term complication is renal disease, which develops in 5% of patients. Renal involvement may manifest itself with haematuria, with or without proteinuria, and occasionally with nephritic or nephrotic syndrome, or with renal failure sometimes associated with a rapidly progressive glomerulonephritis. Urinalysis and blood pressure measurements are mandatory when evaluating a child with HSP. Patients who develop renal involvement generally do so within three months of the onset of rash.[1] Although patients with only haematuria do not develop end-stage renal disease (ESRD), the association of proteinuria and haematuria may be associated with a 15% risk and the combination of nephritic-nephrotic syndrome with a 50% risk of progression to ESRD.[2 3] Children with overt renal disease at presentation are therefore managed early by paediatric nephrologists and may require follow up for at least five years.[4] However, as most of these studies have originated in secondary referral centres on selected populations of children with established nephritis, these recommendations may not necessarily apply to unselected populations of children, most of whom would have no active nephritis on diagnosis.

Furthermore, the follow up of those without initial nephritis, nephrotic syndrome, or renal failure is still recommended to detect renal involvement, and although it is suggested that it need not be five years, the exact duration of follow up remains undetermined.[5] With an incidence of HSP in the population estimated at 14 per 100 000 and with 75% of cases occurring in children aged 2–11 years, with the majority not developing long term renal impairment, a more judicious evidence based approach to selective follow up is needed if resources are to be used appropriately.[6 7]

If the risk of long term renal impairment could be estimated by the presence or absence of renal involvement at diagnosis, and if the time period when renal involvement is very unlikely after HSP diagnosis could be determined, that evidence could be used to identify which children with HSP (without initial nephritic or nephrotic syndrome or renal failure) will need follow up, and if so, for how long. To try to answer these questions we undertook a systematic review of the published literature.

METHODS

Study retrieval and selection strategies

A computerised literature search was carried out using the Cochrane Library (2005, issue 1), Medline (from January 1966 to March 2005), and Embase (from January 1974 to March 2005). The search terms included: (epidemiology OR cohort studies OR follow-up studies OR incidence) AND (purpura;Schoenlein-Henoch {MESH}) AND (complications OR prognosis OR kidney diseases {MESH} OR proteinuria OR hematuria OR glomerulonephritis OR nephritis OR nephrotic syndrome OR hypertension OR kidney failure). The review was focused on published studies in peer reviewed journals and therefore specifically omitted data from the ''grey'' and

Abbreviations: ESRD, end-stage renal disease; HSP, Henoch-Schönlein purpura; NNP, nephritic or nephrotic syndrome

Table 1 Summary of reports

Report	No. patients	Mean age (range), years	Occurrence of urinary findings after HSP	Renal involvement at presentation	Mean follow up (range), years	No. (%) with long term renal impairment
Koskimies *et al*[2]	141	<16	NA	None 102 Haematuria ± proteinuria 31 Nephritis 1 Nephrotic 6 Nephrotic ± nephritis 1 Total 39 (28%)	7.2 (3.0–13.8)	0 (0%) 0 (0%) 0 (0%) 0 (0%) 1 (100%) Total 1 (2.5%)
Garcia-Porrua *et al*[28]	73	6.1 (1–13)	NA	None 32 Haematuria ± proteinuria 33 Nephrotic ± nephritis 8 Total 41	7.7 (1–20)	0 (0%) 0 (0%) 0 (0%) 0 (0%)
Saulsbury *et al*[30]	100	5.9 (1–15)	30 (75%) within 4 weeks 10 (25%) after 4 weeks None after 9 weeks	None 60 Haematuria ± proteinuria 34 Nephritis 6 Total 40 (40%)	(0.1–5)	0 (0%) 0 (0%) 1 (16.6) Total 1 (2.5%)
Kumar *et al*[32]	45	7.6 (2.5–12)	All within 2 months	None 31 Haematuria ± proteinuria 5 Nephritis 6 Nephrotic 3 Total 14	(1–32)	0 (0%) 0 (0%) 0 (0%) 0 (0%) Total 0 (0%)
Stewart *et al*[5]	270	<16	NA	None 215 Haematuria ± proteinuria 37 Nephrotic ± nephritis 18 Total 55	8.3	0 (0%) 0 (0%) 1 death renal 5.5%) Total 1 (1.8%)
Ronkainen *et al*[8]	47	<16	Within a month: 36 After 2 months: 1 After 6 months: 1	NA 5 None 9 Haematuria ± proteinuria 18 Nephrotic ± nephritis 20 Total 38	24.1 (16.4–36.5)	NA 0 (0%) 2 (1%) 7 (35%) (risk 2.5 times higher in females) Total 9 (23.6%)
Lin *et al*[29]	84	6.6 (1.2–11.9)	NA	None 64 Haematuria ± proteinuria 20 Nephrotic ± nephritis 5 Total 25	>1	0 (0%) 0 (0%) 0 (0%) Total 0 (0%)
Chen *et al*[10]	101	(3–17)	1 day: 5 1–7 days: 8 1–2 weeks: 6 2–4 weeks: 10 4–6 weeks: 3 >6 weeks 3	None 66 Haematuria ± proteinuria 29 Nephrotic 3 Nephritis 3 Total 35	2 (0.3–8)	0 (0%) 2 (6.9%) 2 (66.6%) 3 (100%) Total 7 (20%)
Pabunruang *et al*[18]	47	(3–5)	<2 months: 16 <6 months 6	None 25 Haematuria ± proteinuria 22 Total 22	2.6 (1–5)	0 (0%) 0 (0%) 0 (0%)
Calviño *et al*[9]	78	5.5	<3 months: 100%	None 37 Nephrotic 1 Haematuria ± proteinuria 40 Total 41	7	0 (0%) 1 (100%) 0 (0%) 1 (2.4%)
Mintzer *et al*[31]	107	NA	NA	None 76 Haematuria ± proteinuria 30 Nephrotic 1 Total 31	(4–24)	0 (0%) 0 (0%) 0 (0%) 0 (0%)
Dawod *et al*[33]	40	6 (2.2–13)	NA	None 33 Haematuria ± proteinuria 7	0.6 (0.1–5)	0 (0%) Hypertension 1 (14%)

unpublished literature, such as meetings or conferences abstracts, contacts with experts in the field, or data from previously published guidelines. The author examined each paper's title and abstract, the full paper when necessary, and also the reference lists of relevant studies to identify relevant articles, especially when pre-1966. The author decided which studies to be included in the final review.

Eligibility

Studies were included that met the following criteria: (a) cohort studies of unselected children (less than 16 years of age) with HSP; (b) availability in the reports of the details of urinary findings and renal involvement, in particular the time they occurred after the diagnosis of HSP; and (c) availability of renal function follow up in the report.

Table 2 Presentation on diagnosis of HSP and long term renal impairment

	Children		Long term renal impairment		
	No.	%	No.	% (95% CI)	Relative risk (95%)
Total	1133		21	1.8 (1.1 to 2.8)	NA
With normal urine	746	65.8	0	0 (0 to 0.5)	NA
With abnormal urinalysis	387	34.2	21	5.4 (3.3 to 8.3)	NA
Isolated haematuria ± proteinuria	305	78.8	5	1.6 (0.5 to 3.8)	(baseline)
Nephritic or nephrotic syndrome	82	21.2	16	19.5 (11.1 to 31.7)	11.9 (4.1–41.5)

NA, not applicable; CI, confidence intervals.

Case definition

- Isolated haematuria: small amount (+) of haemoglobin on dipstick testing, or greater than 5 red blood cells per high power microscopic field in a centrifuged specimen, or more than 10 red blood cells per microlitre on microscopy.
- Isolated proteinuria: small amount of protein (+) on dipstick testing or proteinuria between 4 and 40 mg/m^2/hour.
- Nephrotic syndrome: nephrotic range proteinuria (greater than 40 mg/m^2/hour or 50 mg/kg/24 hours), with or without oedema and hypoalbuminaemia.
- Nephritic syndrome: haematuria associated with at least one of the following: raised serum urea and creatinine, hypertension, oliguria.
- Renal failure: serum creatinine concentration above the upper limit of normal.
- Long term renal impairment: presence at last follow up of either nephrotic syndrome, nephritis, or renal failure as defined above, or hypertension.

These case definitions were used in all the studies reviewed.

Exclusion criteria

Studies were excluded from analysis if they included selected children with (or without) established HSP nephropathy at diagnosis, if there were no adequate data on urinary findings and renal involvement with time of occurrence after diagnosis, or if no follow up of renal function was available.

Consolidation of all reported data

As isolated haematuria or proteinuria is usually associated with a benign renal prognosis, and as many studies grouped them together in analysing the cohorts, we kept them in a single group of isolated haematuria or proteinuria (IHP) in the absence of nephritic or nephrotic syndrome, or renal failure.[3 6 8–11]

As the presence of nephritic or nephrotic syndrome, or renal failure on diagnosis is associated with a higher incidence of long term renal impairment, and as some reports have grouped nephritic and nephrotic syndrome together in their analysis, we kept them in a single group (NNP).[3 6 8–11]

Statistical analysis

We calculated the total number of children with HSP in the collected studies, including those with or without initial urinary abnormalities, the time of urinary abnormalities to develop after HSP diagnosis, the number and percentage of children developing nephritic or nephrotic syndrome or renal failure, and the number and percentage of children with reduced renal function on long term follow up. With the variable duration of follow up in the studies, acturial or ''survival''-type data analysis was found not to be possible as the time periods for urinary abnormalities observed after the diagnosis of HSP and the time for the observed outcome were not available for each individual case. The only available mode of analysis was therefore simple aggregation of the data according to the blocks of outcome-time given in the studies.

We calculated the cumulative proportion of urinary abnormalities developing over time after diagnosis of HSP by aggregation of the data according to the blocks of outcome-time given in the studies as the time periods for urinary abnormalities observed after the diagnosis of HSP were not available for individual patients.

We calculated the incidence risk (with 95% confidence intervals using Poisson method for rare outcomes) of long term renal impairment to develop after normal or abnormal urinalysis at presentation, or after nephritic or nephrotic syndrome at initial presentation.

RESULTS

Study selection

A total of 34 reports were retrieved. Twenty two articles were excluded from further analysis based on the predefined exclusion criteria: 12 studies with selected cohort of children with established renal involvement,[3 4 10–19] two papers of selected cohorts of children without renal involvement,[5 20] three studies with no time period data for urinary abnormalities,[7 21 22] one article with no follow up information,[23] and four studies with a combination of the above exclusion criteria.[24–27]

Validity criteria

The remaining 12 studies fulfilled the inclusion criteria fully: all were unselected cohorts of children with HSP, all had documentation of the time period for the urinary results, and

Table 3 Time of onset of urinary abnormalities after the diagnosis of HSP: cumulative percentage of abnormalities with 95% confidence intervals (CI)

	Weeks after HSP diagnosis					
	1	2	4	6	8	24
Cumulative percentage	37	54	84	91	90	97
95% CI	18–67	33–85	68–100	62–100	71–100	68–100

What is already known on this topic

- All children with nephritic or nephrotic syndrome, or renal failure on Henoch-Schönlein purpura (HSP) diagnosis are at higher risk of long term renal impairment and need long term follow up
- The outcome and recommended duration of follow up of those without initial nephritic or nephrotic syndrome, or renal failure is not well studied

What this study adds

- Children with normal urinalysis have no long term renal impairment. The risk of long term renal impairment is 12 times higher if the initial presentation is complicated by nephritic or nephrotic syndrome rather than only abnormal urinalysis, and is 2.5 times higher in females than males
- Even if urinalysis is normal at presentation, there is a need to follow up urine testing for the first six months as 97% of children who will have abnormal urine findings would develop them by that time. There is no need to follow up after the first six months those whose urinalysis remains normal, but measurements of serum urea and creatinine need to continue in the presence of continued urinary abnormalities

all included a follow up period with well defined outcomes. The level of evidence of each individual study was estimated at level III.2. There was no selection bias in the reporting, nor attrition bias as, although the duration of follow up between patients was variable in the different reports, it did not differ systematically between children with or without urinary abnormalities at presentation. In addition, the losses to follow up were few and not systematically different between children with or without urinary abnormalities at presentation. No performance or detection bias were identified in the studies as the follow up for and the reporting of predefined outcomes did not differ systematically between children with or without urinary abnormalities at presentation.

Overview of the results

These 12 studies were analysed and their results are summarised in table 1. Five reports came from Europe (two from Finland,[2 8] two from Spain,[9 28] and one from the UK[6]), three from South East Asia (two from Taiwan,[10 29] one from Thailand[18]), two from the USA,[30 31] one from India,[32] and one from the Middle East (Qatar[33]). Three reports date from the 1980s,[2 6 10] five from the 1990s,[29–33] and four were published since 2000.[8 9 18 28] They include a total of 1133 children (number ranging from 40 to 270 children in individual studies), all from secondary care institutions, with a follow up period ranging from a minimum of 6 weeks to a maximum of 36 years (table 1).

Normal urinalysis was found in 65.8% of the children, while proteinuria and/or haematuria occurred in 34.2%, of which only one fifth were in association with nephritic or nephrotic syndrome (NNP). Approximately four fifths of children with abnormal urinalysis had IHP (table 2).

When haematuria or proteinuria developed, it occurred in 85% of cases within 4 weeks of the diagnosis of HSP, in 91% within 6 weeks, and in 97% within 6 months (table 3).

The overall percentage of children who developed long term renal impairment on long term follow up was 1.8%. Long term renal impairment never developed in any child who had normal urinalysis. While it occurred in 5.4% of those who had abnormal urinary findings, 1.6% of those with IHP developed long term renal impairment, while that percentage increased to 19.5% of those who developed nephritic or nephrotic syndrome (table 2).

DISCUSSION

In this review, children with normal urinalysis had no long term renal impairment, confirming previous studies, including a report on a selected cohort of children with normal urinalysis at diagnosis of HSP.[5 8] As the great majority (97%) of children who will have abnormal urine findings would develop them within six months of the initial presentation, even when urinalysis is normal at presentation, urine testing needs to be continued for that period.[18] The proportion of children presenting with IHP was less in this analysis (37%) than in previous studies (67%) and may be related to the grouping of several large unselected cohorts of affected children.[6]

The study also confirmed that the risk of long term renal impairment was low (1.6%) in those with only isolated proteinuria or haematuria, but was much higher (19.5%) if the initial presentation was complicated by nephritic or nephrotic syndrome, with the risk being 2.5 times greater in females than males.[3 8–11]

The strength of analysing several large unselected cohort studies with good follow up for outcomes is tempered by some potential limitations. Some studies did not specify if the urinary or renal abnormalities observed during the follow up period were all related to the first presentation of HSP or may have been associated with relapses, which may render inaccurate the calculations made based on the findings on the initial presentation. It is impossible to be certain that some children with renal involvement at presentation were not followed up more thoroughly and for longer than the others; ascertainment bias cannot therefore be excluded, nor can the theoretical possibility that some patients with no renal involvement at presentation may have developed some urinary abnormalities at a later stage. The definitions of haematuria, proteinuria, nephritic syndrome, nephrotic syndrome, and renal failure were not identical across all studies, but it is unlikely that minimal differences in case definition would have induced significant bias in some reports. The fact that some studies did not differentiate whether haematuria was isolated or was associated with proteinuria could jeopardise the analysis of the observed outcomes, as the presence of proteinuria carries a more severe prognosis on the renal function than isolated haematuria.[34] Similarly, other studies did not differentiate whether nephrotic syndrome occurred with or without nephritis, making the interpretation of outcome fraught with a degree of imprecision. As many children with HSP remain undiagnosed and/or do not present to healthcare workers, all those analysed reports which originated from medical establishments may have inflated the risk, and the true risk of long term renal impairment in children with normal or isolated urinary findings may be even lower than calculated in this review. However, as it is very unlikely that children with overt renal disease do not present for medical care, the calculated risk in those with established nephropathy is probably a reflection of the true risk. As most analysed reports did not specifically report any therapy for renal involvement on diagnosis, it could be assumed that the findings represent the natural history of this vasculitis, but we cannot rule out the role, if any, of any therapy which had not been reported. A main limitation in this review is the

unavailability, for each individual case, of the time periods for urinary abnormalities observed after the diagnosis of HSP and the time for the observed outcome, precluding an acturial or ''survival''-type data analysis and only allowing simple aggregation of the data according to the blocks of outcome-time given in the studies. In addition, the variable duration of follow up in the studies and the only remaining option of consolidating outcome data available at very different follow up periods does not truly reflect the prognosis, as the absence of nephropathy after two years in one study has a completely different meaning than the same outcome in another study spanning 20 years. Only a large prospective cohort study with a long follow up period could provide a more reliable survival analysis and address these inherent weaknesses.

Despite these limitations, and until large prospective studies have been completed, a practical algorithm may be suggested as a result of this review and the reports on which it was based. At diagnosis and at each HSP recurrence, blood pressure measurement and urinalysis need to be carried out. If haematuria and/or proteinuria is found, serum urea and creatinine determination will be needed. In case of normal urinalysis or if there is IHP without NNP, a periodic check of urinalysis will be needed up to six months after diagnosis. There is no need to follow up after the first six months those whose urinalysis remains normal, but measurements of serum urea and creatinine need to continue in the presence of continued IHP. In case of NNP, a paediatric nephrologist needs to be consulted as urgent evaluation is necessary and long term renal follow up will be definitely needed, even after resolution of the nephritis, especially in affected girls as they will need monitoring of renal function and blood pressure during and after future pregnancies.[8]

Competing interests: none

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